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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,992	BECK ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments filed October 2, 2008 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 31-50 are pending in this application.

Claims 31-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lofftson U.S. Patent No. 5,472,954, Remington's Pharmaceutical Sciences (U) and Lipari U.S. Patent No. 4,383,992 and further in view of Dziabo et al. U.S. Patent No. 5,424,078.

Lofftson et al. teach an ophthalmic composition (column 18, lines 8-12) comprising a cyclodextrin, such as the sulfobutyl ether of β cyclodextrin (column 6, line 60) and an anti-inflammatory steroid (column 19, lines 16-39), such as prednisolone (see table 10, column 28). The ophthalmic cyclodextrin composition has water added in addition to the active ingredient along with pH adjusters, buffers and preservatives, in a sterile isotonic buffered aqueous solution (column 19, lines 24-31).

Lofftson et al. does not teach the acetate salt of prednisolone.

Lofftson et al. teach that cyclodextrins are capable of forming inclusion complexes with a wide variety of hydrophobic molecules by taking up a whole molecule or some part of it into the cavity (column 2, lines 5-8). Lofftson et al. describes the solubilizing effects of cyclodextrins. Although Lofftson et al. does not specifically describe prednisolone acetate, one would have been motivated to employ prednisolone acetate in the cyclodextrin ophthalmic solution of Lofftson et al. motivated by the teaching of Lipari below and by the teaching of Remington's Pharmaceutical Sciences who teaches that prednisolone is slightly soluble in water but prednisolone acetate is practically insoluble in water. It would have been made obvious to one of ordinary skill in art at the time it was made to employ prednisolone acetate in the ophthalmic composition of Lofftson et al. Such a modification would have been motivated by the reasoned expectation of producing an ophthalmic composition that will be solubilized in an aqueous solution and which has enhanced effectiveness due to the complexation with the cyclodextrin carrier for comprehensively treating persons suffering from ophthalmic afflictions. In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. This motivation may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Here, filtered through the nature of the problem to be solved, the prior art (Remington's Pharmaceutical Sciences) disclosed that prednisolone acetate is practically insoluble in water, and that this problem can be

addressed by employing the known solubilizing agent, cyclodextrin or sulfobutylether β cyclodextrin, and a preservative as taught by Lofftson et al.. Accordingly, there was clear motivation to combine the prednisolone acetate and cyclodextrin derivatives with a preservative agent in an aqueous ophthalmic composition.

Lipari teaches an ophthalmic liquid composition comprising prednisolone acetate (column 1, lines 20-24) and a cyclodextrin derivative, β cyclodextrin (see abstract), in a solution (column 1, line 59 to column 1, line 6). The composition increases partitioning of the steroid compound into the cornea with an increased therapeutic response (column 3, lines 65-68).

Lipari lacks a teaching of a preservative and it does not teach an ophthalmically acceptable tonicity level, pH and buffer.

Dziabo et al. teach an ophthalmic composition preserved with a stabilized chlorine dioxide preservative with an ophthalmically acceptable tonicity component and a buffer to maintain the pH of the ophthalmic formulation within the physiological range (see abstract). It would have been obvious to one of ordinary skill in the art at the time it was made to employ chloride dioxide as a preservative in an ophthalmic preparation motivated by the teaching of Dziabo et al. who employs stabilized chlorine dioxide as a preservative for ophthalmic preparations and teaches that ophthalmic preparations must have ophthalmically acceptable tonicity and buffer to maintain the pH of the ophthalmic formulation within the physiological range and Lipari who teaches that prednisolone acetate is made soluble for ophthalmic use by employing β cyclodextrins. The method of preserving ophthalmic agents was recognized as part of the ordinary capabilities of

one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known composition that was ready for improvement and the results would have been predictable to one of ordinary skill in the art. The gap between the Lipari's ophthalmic composition of prednisolone acetate and cyclodextrin preserved with Dziabo et al.'s ophthalmic preservation system and the instant invention is simply not so great as to render the composition and method of use nonobvious to one reasonably skilled in the art.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ chloride dioxide as a preservative in an ophthalmic preparation motivated by the teaching of Dziabo et al who employs stabilized chlorine dioxide as a preservative and acceptable tonicity and buffers to maintain the pH for ophthalmic preparations.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6,358,935. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the description of the particular components claimed. For instance, conflicting claim 1 requires an active therapeutic agent in combination with a cyclodextrin and a preservative wherein the preservative is stabilized chlorine dioxide or sorbic acid. The portion of the patent that supports conflicting claims 1-18 teaches that the active agents include prednisolone acetate (column 6, line 10). Instant claims 31-50 would be encompassed by the conflicting claims. It would have been obvious to anyone of ordinary skill in the art that the claims overlapped in scope in this manner. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

Claims 31-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,723,353. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same

subject matter, differing only in the description of the particular components claimed. For instance, conflicting claim 1 requires an active therapeutic agent in combination with a cyclodextrin and a preservative wherein the preservative is stabilized chlorine dioxide. The portion of the patent that supports conflicting claims 1-13 teaches that the active agents include prednisolone acetate (column 6, line 11). Instant claims 31-50 would be encompassed by the conflicting claims. It would have been obvious to anyone of ordinary skill in the art that the claims overlapped in scope in this manner. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

Response to Declaration

The Declaration under 37 CFR 1.132 filed October 2, 2008 is insufficient to overcome the rejection of claims 31-50 based upon Lofftson U.S. Patent No. 5,472,954, Remington's Pharmaceutical Sciences (U) and Lipari U.S. Patent No. 4,383,992 and further in view of Dziabo et al. U.S. Patent No. 5,424,078 as set forth in the last Office action because: It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. The examples that are referenced in the Declaration are drawn to a specific amount of chlorine dioxide preservative in 0.0075 to 0.15% and/or a specific amount of potassium sorbate preservative in 0.05 to 0.5% along with the specific cyclodextrin sulfobutylether β

cyclodextrin in the specific amount of 8%. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims which are significantly broader in scope because they are drawn to any cyclodextrin and to a chlorite preservative and any sorbate and there are no amounts of the agents recited. See MPEP § 716. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Response to Arguments

Applicant asserts that the Loftsson reference discusses a very large number of compounds (drugs, food additives, cosmetic additives and agrochemicals; see e.g., column 4, lines 1 and 2) which, Loftsson claims, may be formulated with a very large number of cyclodextrin derivatives and a very large number of selected polymers to enhance their solubility or decrease their water lability. A list of various cyclodextrins is disclosed in column 6; a large list of polymers is mentioned e.g., in column 7; a very large list of compounds to be complexed with the cyclodextrin and polymer is listed in columns 7-13. In response, Loftsson teaches the preferred aspect of the invention is a steroid, particularly an anti-inflammatory steroid (glucocorticoid) see column 11, lines 58-62. Further, the instant claims are directed to "cyclodextrins" in general and only instant claims 40 and 50 are directed to the specific cyclodextrin that is supported by the examples In the specification. Regarding the list of polymers recited by Loftsson, the

claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts, such as polymers.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant asserts that none of the prior art discloses that a cyclodextrin-containing composition is not effectively preserved using many of the traditionally used ophthalmic preservatives, such as quaternary ammonlum compounds such as benzalkonium chloride (BAC). In response, Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. In the instant case, Examples 1 and 2 (page 16) comprise sulfobutylether β cyclodextrin and stabilized chlorine dioxide, but do not contain prednisolone acetate. The compositions passed the USPET, composition 1 failed the EP-A and EP-B test, Composition 2 failed the EP-A and passed the EP-B. Examples 3-7 comprise BAC and hydroxybutyl β cyclodextrin. compounds 8 and 9 comprise only BAC. 3-7 fail USPET test and 8 and 9 pass. None

of 3-9 contains prednisolone acetate. Skipping ahead, compositions 20 and 21 comprise prednisolone acetate 0.1%, sulfobutylether β cyclodextrin 8% and stabilized chlorine dioxide 0.15% and 0.0075% respectively. Compositions 20 and 21 both pass the USPED but both fail the EP-A and EP-B tests. The only composition to pass all three tests is composition 33 comprising prednisolone acetate 0.1%, sulfobutylether β cyclodextrin 8% and potassium sorbate, 0.5% with the specific pH of 4.5. Thus the evidence of nonobviousness is not sufficient to rebut the evidence of obviousness.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

December 17, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614